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EXAMINER

SCHNIZER, RICHARD A

ART UNIT

PAPER NUMBER

1635

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/328,975

Applicant(s)

WOLFF ET AL.

Examiner

Richard Schnizer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 10 and 12-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10 and 12-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

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DETAILED ACTION

An amendment and the Declaration of James E. Hagstrom were received and entered as Paper No. 11 on 9/10/01. Claim 19 was added as requested. Claims 1-8, 10, and 12-19 are pending and under consideration in this Office Action.

In Paper No. 3 an election of species was required by the Office. Applicant elected the species succinylated PLL in paper No. 6. This restriction requirement is hereby withdrawn. All species are under consideration in this Office Action.

Rejections Withdrawn

The rejection under 35 USC 112, first paragraph of claims 1-7 is withdrawn because the claims read on at least one enabled process other than gene therapy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

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in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As amended claim 13 requires a complex in which a polycationic polymer and a polyanionic polymer each must be copolymers. Applicant failed to identify any passage in the specification that provides literal support for this combination of limitations. It is noted that 37 CFR 1.121(b)(2)(iii) requires that:

Each amendment when originally submitted must be accompanied by an explanation of the support in the disclosure of the patent for the amendment along with any additional comments on page(s) separate from the page(s) containing the amendment.

Because there appears to be no support in the specification for the claim as amended, it represents new matter.

Enablement

Claims 2, 3, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 2 and 3 are directed to a method which requires the formation of a complex between a nucleic acid and a polymer, wherein the complex has a net charge less negative than the nucleic acid. The claims then require addition of a charged polymer ~~that~~ to that complex, wherein addition of a sufficient amount of the charged polymer results in a

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complex having a net charge less negative than the previous complex. Claims 2 and 3 require that this charged polymer must be a polycation. The specification teaches that a polycation must have a net positive charge. See page 12, lines 20 and 21. It is impossible to add "a sufficient amount" of the charged polymer of claims 2, and 3 to increase the value of the negative charge on the complex, because the charged polymer of claim 2 must have a net positive charge. Thus one of skill in the art could not make the complex required for practice of the claimed invention without undue experimentation.

Claim 17 is a complex formed from the combination of a nucleic acid and a polymer (succinylated PLL, succinylated PEI, polyglutamic acid polyaspartic acid, DNA, RNA, negatively charged proteins, etc.), wherein the complex has a net charge which is less negative than that of the nucleic acid. One of skill in the art cannot form a complex having a net charge less negative than one of its substituents by adding to that substituent a compound with a net negative charge. Thus one of skill in the art could not make the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-7 and 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 and 15-18 are indefinite for the following reasons. These claims, in step b) require the following: “attaching a charged polymer to the complex in sufficient amount to change the complex net charge wherein the complex has a net charge more negative than the complex in the previous step”. This passage is unclear because the method steps cannot result in the recited process. The complex in step a) has a given net charge. Attaching a charged polymer to that complex does not change the net charge of the complex, it results in a new complex that has a net charge different than the previous complex. It is suggested that step b) should be amended to read “attaching a charged polymer to the complex of step a) in sufficient amount to form a new complex having a net charge more negative than the complex in step a)”.

Claim 17 is indefinite because it recites a non sequitur. Specifically, it requires first that “the polymer” is selected from the group **consisting** of PLL and PEI, but then allows the polymer to comprise a variety of compounds that are not PLL or PEI, including succinylated PLL, succinylated PEI, polyglutamic acid polyaspartic acid, DNA, RNA, and negatively charged proteins, etc.

Claim Rejections - 35 USC § 102

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 10, 12, 14-16, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Erbacher et al Drug Deliv. 4:173-179, 1997), as evidenced by Basu et al (Biochim. Biophys. Acta 533 (1): 66-73, 1978), and GenBank Accession No. CAA41735.

Erbacher teaches compositions comprising polylysine/DNA complexes to which a negatively charged protein, lactosylated bovine serum albumin (BSA), was bound in a solution of neutral pH (DMEM). See abstract; page 175, first full paragraph of column 1; and Fig. 1 on page 175. BSA is a polyanionic polymer at neutral pH as evidenced by Basu et al (Biochim. Biophys. Acta 533 (1): 66-73, 1978), who teaches that BSA has a pI of either 4.8 or 5.6, and as evidenced by the sequence disclosed in GenBank Accession No. CAA41735. The complex is used to deliver nucleic acids to cells in vitro. See abstract.

Thus Erbacher anticipates the claims.

Claims 8, 10, 12, 14-16, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Plank et al (J. Biol. Chem 269(17): 12918-12924).

Plank teaches compositions comprising polylysine/transferrin/DNA complexes, to which are added negatively charged proteins. See abstract; Table I on page 12920 which gives the

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sequences of the peptides; Fig. 3, panel A on page 12922. Planck also teaches a process for delivering these complexes to cells *in vitro*. See abstract, and Fig. 3, panel (c) on page 12922.

Thus Plank anticipates the claims.

Claims 8, 10, 12, 14, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Gao et al (HUMAN GENE THERAPY, (1993 Feb) 4 (1) 17-24) or Kupfer et al (HUMAN GENE THERAPY, (1994 Dec) 5 (12) 1437-43).

Gao and Kupfer each teach a method of delivering a nucleic acid to a cell *in vivo* comprising a forming a complex consisting of three types of polymers, a negatively charged nucleic acid, a polycation, and a negatively charged protein, transferrin, and delivering the complex to cells in a mammal *in vivo*. See abstracts.

Thus Gao and Kupfer each anticipate the claims.

Claims 8, 10, 12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Boussif et al (Proc. Nat. Acad. Sci. 92:7997-7301, 8/1995).

Boussif teaches a method of making nucleic acid/PEI complexes. The nucleic acid can be considered to be the polyanion of the claims, and PEI is the polycation. See abstract, and paragraph bridging columns 1 and 2 on page 7298.

Thus Boussif anticipates the claims.

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Claims 8, 10, 12 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Kabanov et al (US Patent 5,656,611, issued 8/12/97).

Kabanov teaches a complex comprising nucleic acids complexed with a polycationic block copolymer. See column 3, lines 1-37, especially lines 1 and 34-37. The nucleic acid can be considered to act as the polyanion polymer, thus Kabanov anticipates the claims.

Claims 8, 10, 12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al (Nucl. Acids Res. 25(10): 1950-1956, 5/1997).

Baker teaches compositions comprising nucleic acids complexed with either polylysine/adenovirus conjugates or polyethyleneimine/adenovirus. The nucleic acid can be considered to act as the polyanion polymer recited by claims 8 and 10. Polylysine and polyethyleneimine are the polycations.

Thus Baker anticipates the claims.

Claims 8, 10, 12, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Katayose et al (Bioconj. Chem. 8:702-707, 1997).

Katayose teaches a complex comprising a nucleic acid, polylysine, and polyaspartic acid. See abstract, and Fig. 5, panel B which discloses an intermediate in an exchange reaction, wherein the intermediate comprises DNA, PLL, and polyaspartic acid.

Thus Katayose anticipates the claims.

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Response to Arguments

Applicant's arguments, and the Declaration of James E. Hagstrom filed 9/10/01 have been fully considered as they might apply to both the original and new grounds of rejection, but they are unpersuasive.

With respect to the Boussif, Kabanov, and Baker references, Applicant argues that the cited art does not anticipate the claims because it does not teach a double recharging process. This is unpersuasive because the rejected claims require no such process.

The Declaration of James E. Hagstrom has been fully considered but is unpersuasive. The Declaration was intended to show that the Applicant was in possession of the claimed invention by June of 1994. The rejections stand because the Declaration discloses only experiments in which nucleic acids were recharged with cationic histones. Note that Claims 8, 10, 12, and 14-19 allow for cationic compounds other than histones. In fact none of these claims recites histones as a polycationic polymer. In particular, claims 10 and 16 require that the polycation must be PLL or PEI. The Declaration fails to establish that Applicant was in possession, prior to the time of filing, of any claimed composition or method other than those comprising complexes between histones and nucleic acids. For these reasons, the rejections are maintained. The rejections may be overcome by limiting the identity of the polycation to histone. Applicant should confirm that such an amendment would not introduce new matter into the disclosure.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Gao (1993) or Kupfer (1994), in view of Plank (1994).

Gao and Kupfer each teach a method of delivering a nucleic acid to a cell *in vivo* comprising a forming a complex consisting of a nucleic acid, polylysine, and transferrin, and delivering the complex to cells in a mammal *in vivo*. See abstracts. These references do not teach the addition of a charged polymer to the DNA/polylysine/transferrin complex.

Plank teaches compositions comprising polylysine/transferrin/DNA complexes, to which are added negatively charged proteins. See abstract; Table I on page 12920 which gives the sequences of the peptides; Fig. 3, panel A on page 12922.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods of Gao or Kupfer by adding the negatively charged proteins of Plank. One would have been motivated to do so because these proteins allow escape from the endosomal/lysosomal pathway, thereby allowing one to avoid degradation of DNA in the

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lysosomes, and enhance gene expression. See first sentence of abstract, and first sentence and lines 14-16 of first full paragraph on page 12918, column 1.

Claim 6 is included in this rejection, because several of the proteins of Plank can be considered to comprise block copolymers. For example, INF3DI, INF3DI2, INF3DI3 and INF5 consist of inverted repeats of amino acid sequences, and GALA, GALA-GLF, GALA-INF1, and GALA-INF3 comprise repeats of the blocks EA and LA. See Table I on page 12920.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.



JAMES KETTER
PRIMARY EXAMINER